Percent carboxyhemoglobin in resting humans exposed repeatedly to 1,500 and 7,500 ppm CO

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TIKUISIS, P., F. BUICK, AND D. M. KANE. *Percent carboxyhemoglobin in resting humans exposed repeatedly to 1,500 and 7,500 ppm CO.* J. Appl. Physiol. 63(2): 820–827, 1987.—Eleven nonsmoking male resting subjects were exposed to two transient CO profiles to examine whether the resultant carboxyhemoglobin (HbCO) differs with CO concentration for a fixed total CO dose and to determine the predictive capability of the theoretical model of Coburn et al. (*J. Clin. Invest.* 44: 1899–1910, 1965) using measured alveolar ventilation. One profile consisted of five sequential exposures to 1,500 ppm CO for 5 min each and spaced 3 min apart. The other consisted of five sequential exposures to 7,500 ppm CO for 1 min each and spaced 7 min apart. The subjects, therefore, were exposed to the same overall nominal dose of 37,500 ppm·min. During the experiment, the subject's ventilatory functions and respiratory gases were recorded continuously, and the resultant HbCO% was measured in venous blood samples by gas chromatography. Mean increase (±SD) in HbCO% per exposure was 2.08 ± 0.27% for the 1,500 ppm CO exposures and 2.05 ± 0.29% for the 7,500 ppm CO exposures with no significant difference between the two. When the measured values of the subject's alveolar ventilation were applied to the theoretical model of Coburn et al., the predicted rate of HbCO% formation was found to agree with the experimental results.

carbon monoxide uptake; alveolar ventilation; pulmonary diffusing capacity

STUDIES ON THE RATE OF FORMATION of blood carboxyhemoglobin (HbCO) resulting from exposure to low steady-state and high transient concentrations of CO have included predictions from mathematical models such as that described by the equation of Coburn, Forster, and Kane (CFK) (4). Although the CFK equation was originally developed for the study of the endogenous production of CO, it has been widely adopted for predicting the rate of whole-body HbCO formation (2, 8, 10, 14, 17, 18). There are two aspects in the use of this model, however, that have not been fully addressed.

First, does the resultant carboxyhemoglobin saturation (HbCO%) from a particular total dose, i.e., parts per million per minute, vary if the concentration of CO varies over the exposure period? Jones et al. (9) found no significant difference in the diffusing capacity for CO between three concentration levels ranging from <1 to 3,000 ppm. However, in this study using the rebreathing method, the total dose and consequently the resultant HbCO% was not the same between levels. Other investigators have also exposed subjects to varying levels of CO, in some cases as high as 35,600 ppm (16), but no systematic comparison of the resultant HbCO% from different concentrations of CO has been conducted. It is of physiological and practical importance to know whether the final HbCO% would differ if, for example, the exposure were to x ppm CO for y min, compared with $y \times x$ ppm CO for 1 min, thus exposing the subject to the same total dose. If there is no difference, then in applying the CFK equation to situations where the CO level varies considerably over an acute exposure period, the average concentration of inspired CO during that time is sufficient for the HbCO% prediction.

Second, what is the required accuracy of the value of the alveolar ventilation ($\dot{V}_A$) assigned to the CFK equation to make the model's predictive capability valid? $\dot{V}_A$ is one of the key parameters that governs the rate of HbCO% formation as demonstrated by Peterson and Stewart (14), yet in the applied and occupational literature, its value is often assumed (2, 18), estimated, or not reported. Peterson and Stewart (14) used tidal volume-dead-space relationships to determine $\dot{V}_A$; Tyuma et al. (17) used anthropometric relationships; and Jourmard et al. (10) used energy expenditure relationships. Hauck and Neuberger (8) reported to have measured $\dot{V}_A$, but no values were given nor details on how this was accomplished. Furthermore, in the derivation of the CFK equation (4), the value of $\dot{V}_A$ was explicitly expressed for STPD conditions, however, only Tyuma et al. (17) used STPD conditions. Bernard and Duker (2) used the BTPS condition, and in Refs. 8, 10, 14, and 18, the conditions used were not stated. Units in BTPS are numerically ~21% greater than in their STPD form. Use of the BTPS numerical values for $\dot{V}_A$ in the CFK equation would result in an overprediction of the rate of HbCO% formation by ~15% in subjects at rest.

The present study was undertaken to address these two aspects. Resting human subjects were exposed to two transient concentrations of CO, of equal total dose, to compare the resultant formation of HbCO. In applying the CFK equation, the measured value of $\dot{V}_A$ was used.

THEORETICAL MODEL

The model for describing the rate of change of [HbCO] is given by (4)

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$$\frac{d[HbCO]}{dt} = \frac{\dot{V}CO}{Vb} + \frac{1}{Vb \cdot \beta}\left(P_{ICO} - [HbCO]_o \frac{P_{c_{O_2}}}{[HbO_2]M}\right) \quad (1)$$

where

$$\beta = \frac{1}{D_{LCO}} + \frac{(P_B - 47)}{\dot{V}_A} \quad (2)$$

and where $[HbCO]_o$ is the original concentration of CO bound to hemoglobin (ml STPD/ml blood) and assumes that total body CO stores are proportional to blood HbCO% (4); $\dot{V}CO$ is the rate of the endogenous production of CO (ml STPD/min); Vb is the effective blood volume (ml); P_{ICO} is the saturated inspired CO pressure (Torr); $P_{c_{O_2}}$ is the mean O_2 tension (Torr) in the pulmonary capillary blood; M is the Haldane ratio of the affinity of blood for CO compared with that for O_2; $[HbO_2]$ is the concentration of O_2 (ml STPD/ml blood) bound to hemoglobin in the pulmonary capillary blood; D_{LCO} is the pulmonary diffusing capacity of CO (ml STPD $\cdot$ min^{-1} $\cdot$ Torr^{-1}); P_B is the barometric pressure (Torr); and $\dot{V}_A$ is the alveolar ventilation (ml STPD/min).

In the original solution of the CFK equation (*Eq. 1*), it was assumed that $[HbO_2]$ was constant. This was appropriate considering that the original purpose of the CFK equation was to study the endogenous production of CO and the values of [HbCO] were relatively low when compared to those of $[HbO_2]$. However, when the inspired CO concentration is large enough to cause significant increases in the value of [HbCO], the decrease in $[HbO_2]$ must be taken into account. This decrease can be described by (14)

$$[HbO_2] = 1.38\ [Hb] - [HbCO] \quad (3)$$

where [Hb] is the hemoglobin concentration (g/ml blood). With the substitution of *Eq. 3*, the CFK equation (*Eq. 1*) becomes nonlinear. To solve the nonlinear form of the CFK equation, numerical integration can be used.

METHODS

Subjects. Experiments were conducted with eleven nonsmoking male volunteer subjects, 27–35 yr old. In accordance with the Defence and Civil Institute of Environmental Medicine Human Ethics Committee guidelines for human experimentation, each subject was fully informed of the experimental procedure before giving his consent. Before the experiment, the subject was medically screened and verified to have normal pulmonary function and D_{LCO}. A physician attended to the subject during the experiment.

Techniques. Pressure in the mask cavity was measured via a luer-lok port with a Statham differential pressure transducer (model PR-23-56-300, Hato Rey, PR) and Gould universal amplifier (Cleveland, OH). Expired flow was measured by a heated Fleisch pneumotachograph (no. 00, Instrumentation Associates, New York, NY), a Statham differential pressure transducer (model PM15E), and a Gould universal amplifier. The pneumotachograph was calibrated using a rotameter. Mask cavity pressure and expired flow were used as markers on the polygraph for the respiratory cycle and expired gas collection in a 120-liter capacity Tissot spirometer, respectively. The electrocardiogram was displayed on a Tektronix electrocardiogram monitor (model 408, Beaverton, OR). All respiratory gases were analyzed on a breath-by-breath basis by a mass spectrometer (Perkin-Elmer MGA 1100, Pomona, CA). The O_2, CO_2, and N_2 channels were calibrated before each experiment using certified gas standards. All statements to measured CO in this report actually refer to $C^{18}O$. The CO gas mixtures were commercially prepared with pure, medical grade gases to produce 0.15 or 0.75% $C^{18}O$, 21% O_2, and balance N_2 (Matheson Gas, Whitby, Ontario). The $C^{18}O$ breathing gases were also used for calibrating the $C^{18}O$ channel on the mass spectrometer. That channel was calibrated before the first $C^{18}O$ exposure and verified with 0.45% $C^{18}O$ after the second and fourth exposures. All analog outputs were recorded continuously on a multichannel paper recorder (Gould ES-1000) and on FM magnetic tape (Hewlett-Packard 3968A, Waltham, MA).

HbCO% determination. Blood HbCO% was measured using both gas chromatography (GC) and CO-oximetry, for accuracy and speed, respectively. The blood samples were analyzed by CO-oximetry (model 2500, CO-oximeter, Corning) within 2 min of being drawn, and the result was used to monitor the HbCO% increase so as not to overexpose the subject (an upper limit of 15% HbCO was allowed for the study). Aliquots of 0.25 ml of the blood samples were also sealed into reaction vials for subsequent analysis by the GC method. A hemolyzing solution of 0.5 ml was injected into each reaction vial to release the CO from HbCO. A 0.1-ml aliquot of the vial headspace was injected in a GC (Carle 211) and CO detected, after catalytic conversion to methane, using flame ionization. The area of the chromatographic peak was then used to determine the blood HbCO% level (11). Calibration was carried out using 500 ppm CO in a N_2 primary standard gas mixture. Every sixth blood sample was run in duplicate to check method repeatability.

Experimental setup and procedures. The subject rested in a semirecumbent position. An intravenous catheter with a heparin lock was inserted into a vein in the antecubital fossa for blood samples. An aviator's oronasal oxygen mask was worn by the subject. With the two unidirectional valves, the mask had a dead space of ~100 ml. Breathing gas was delivered to the mask from gas impermeable bags, which were inflated by compressed gas cylinders. The three bags contained room air, 1,500 ppm CO, and 7,500 ppm CO, respectively. The low-resistance circuit assured natural and uninterrupted breathing. Inspirate selection was performed during the subject's expiration with a Hans Rudolf four-way directional stopcock mounted out of his view. Respired gases were sampled by the mass spectrometer at a rate of 1.0 ml/s through a 2-m-long capillary tube from within the mask near the subject's lips. With a second stopcock, the subject's expired gas was either vented into the room or, when exposed to CO, collected in the Tissot spirometer for minute ventilation and mixed expired gas analysis. All Tissot gas was checked for volume by exhausting it through a Singer dry gas meter. With the mask positioned, maintenance of slight positive/negative static

airway pressure confirmed the breathing circuit to be leak free.

The subjects were exposed to two different intermittent CO profiles on separate days but in random order. As illustrated in Fig. 1, the profiles consisted of five sequential exposures either to 1,500 ppm CO for 5 min each, spaced 3 min apart, or to 7,500 ppm CO for 1 min each, spaced 7 min apart. Thus both profiles resulted in the same total dose of 37,500 ppm·min CO inhaled by the subjects after 37 min. Between exposures, the subject was switched to breathe normal air.

Blood samples of 3.5 ml were taken to measure HbCO% and to determine each subject's mean hemoglobin concentration. These samples were drawn every 4 min at the times indicated by the arrows in Fig. 1. With this schedule, HbCO% was measured 1 min before an exposure and 2 min after an exposure for both inspired CO concentrations. This schedule also prevented the subject from recognizing the CO profile used on that day.

The subject's inspired gas was switched to 100% O_2 after the last blood sample was drawn, 43 min after the beginning of the first exposure (see Fig. 1). When the subject's HbCO% was <5%, as determined by further blood sampling, pure O_2 breathing stopped. At the conclusion of the experiment, the subject was asked whether he recognized the concentration level and timing of the CO exposures and whether he felt any symptoms.

ANALYSIS

Potential differences were tested using Student's *t* test or analysis of variance at the 0.05 level of statistical significance.

Pulmonary diffusing capacity for CO. D_{LCO} was determined during the experiment by the steady-state method using the expression (7)

$$D_{LCO} = (F_{ICO}/F_{ACO} - 1)\dot{V}_A/(P_B - 47) \quad (4)$$

where F_{ICO} and F_{ACO} are the steady-state dry fractional concentrations of CO in the inspired and alveolar gas samples, respectively. These values were obtained from the peak inspired and the end-tidal steady-state values measured from the mass spectrometer recordings. End-tidal steady-state values of CO were assumed to represent the alveolar values.

Alveolar ventilation. $\dot{V}_A$ was determined on the basis of CO_2 elimination according to (5)

$$\dot{V}_A = \dot{V}_{CO_2}/F_{A_{CO_2}} \quad (5)$$

where $\dot{V}_{CO_2}$ is the rate of CO_2 production and $F_{A_{CO_2}}$ is the dry fractional concentration of CO_2 in the alveolar gas measured from the peak end-tidal values recorded by the mass spectrometer. $\dot{V}_{CO_2}$ was determined by the product of minute ventilation ($\dot{V}_E$) and the dry fractional concentration of CO_2 ($F_{E_{CO_2}}$) in the mixed expired gas. $F_{E_{CO_2}}$ was obtained from the mass spectrometer readings of the mixed-expired gas collected in the spirometer after each exposure. $\dot{V}_E$ (liters BTPS/min) was determined by

$$\dot{V}_E = V_E \times (60/t_c) \times (P_B - P_{H_2O}) \times 310/(P_B - 47)/(273 + T) \quad (6)$$

where V_E is the volume (liter ATPS) of expired gas under spirometer conditions, t_c is the collection time(s) of the expired gas, P_{H_2O} is the saturated water vapor pressure (Torr) in the spirometer, and T is the temperature (°C) of the gas in the spirometer. $\dot{V}_E$ was determined directly from the spirometer bell displacement, and a correction for the amount of gas lost to the mass spectrometer was applied.

HbCO%. Only the results obtained by the GC method were used in data analysis. Previous work (11) has shown that CO-oximeter HbCO% readings are biased high at HbCO < 8% but that the GC method agrees with calculated HbCO% for blood standards prepared by mixing CO-saturated and unsaturated blood in known proportions over the range of 0.5 to 100% HbCO. In view of this, CO-oximetry was only used as a rapid monitor of

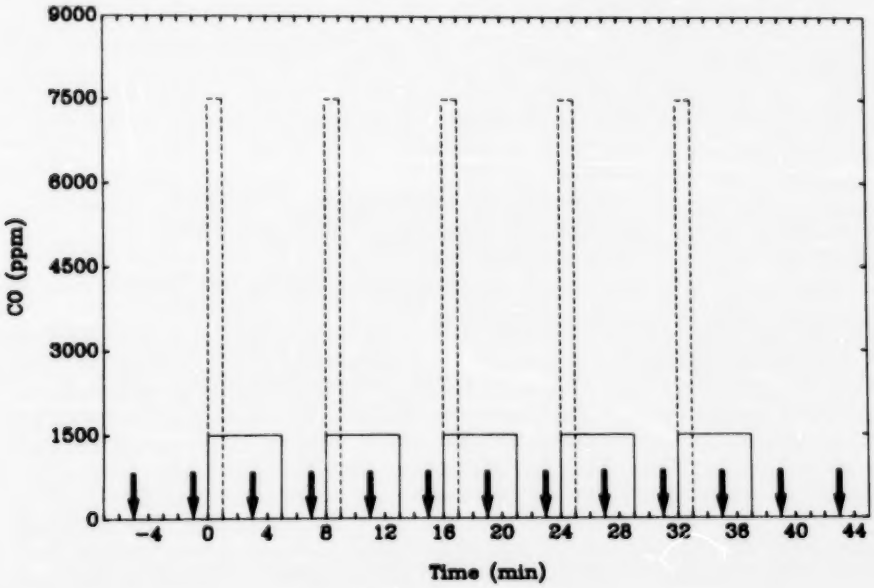

FIG. 1. Profiles for exposures to 1,500 (*solid lines*) and 7,500 ppm (*dashed lines*) CO concentration levels. Both profiles give same overall nominal dose of 37,500 ppm·min. *Arrows* indicate when blood samples were taken for percent carboxyhemoglobin analysis.

the rise in HbCO% during the experiment.

CFK model prediction. The CFK equation was solved by applying the fourth-order Runge-Kutta numerical integration (12) technique. The predicted increase in HbCO% for each subject in each exposure was based on his initial HbCO measured at 1 min before the first exposure, on the inspired CO concentration, on his $\dot{V}_A$ and $D_{L_{CO}}$, and the durations of the exposure and nonexposure periods. The value used for $\dot{V}_A$ was measured separately for each exposure and nonexposure period by use of *Eq. 5*. The value of $D_{L_{CO}}$ was determined separately for each exposure to CO using *Eq. 4*; however, the subject's mean value from the five exposures was used in the model prediction due to the variability in the measure of $D_{L_{CO}}$.

$P_{I_{CO}}$ was determined by

$$P_{I_{CO}} = F_{I_{CO}} \times (P_B - 47) \quad (7)$$

where $F_{I_{CO}}$ is the steady-state dry fractional concentration of CO in the inspired gas sample.

The mean tension of O_2 in the pulmonary capillary was determined from (14)

$$P_{c_{O_2}} = P_{I_{O_2}} - 49 \quad (8)$$

where $P_{I_{O_2}}$ is the saturated inspired O_2 pressure (Torr). For the experimental conditions, its value was determined from

$$P_{I_{O_2}} = 0.21\ (P_B - 47) \quad (9)$$

Vb was estimated according to (1)

$$Vb = 0.0003669H^3 + 32.19W + 604 \quad (10)$$

where H is the subject's height (cm) and W his weight (kg). $\dot{V}_{CO}$ and M were assigned the values of 0.007 ml STPD/min and 218, respectively (14).

RESULTS

Subject questionnaire. The worst symptom reported at the conclusion of the experiment was a slight frontal headache, which was attributed to discomfort of the tight mask fit. Only two subjects who were well acquainted with the experimental procedure could approximate when gas switching took place, but the concentration of CO used could not be sensed.

Measurements. Duplicate HbCO measurements were made using the GC method on 59 of the 286 blood samples drawn. The mean differences between repeated measurements were 0.08 ± 0.05 (SD), 0.14 ± 0.11, and 0.16 ± 0.14% for the blood samples with HbCO% <5% (n = 17), between 5 and 10% (n = 20), and >10% (n = 22), respectively. The overall mean difference between repeated measurements was 0.13 ± 0.11%. This was within the 5% variation expected over the HbCO range of 0.5–20% for the GC method (11). The 286 pairs of data points generated a regression line HbCO(CO-oximetry) = 1.013 × HbCO(GC) + 1.28, with a r^2 of 0.989. This confirmed the high bias of the CO-oximetry method.

A typical recording of ventilatory function and respiratory gases for an exposure to 7,500 ppm CO is shown in Fig. 2. At the top of the recording, a trace of mask pressure is shown followed by a trace of the expiratory flow. The next trace shows the dry fractional concentration of $C^{18}O$ in the gas sample drawn continuously from near the mouth. The inspired CO reached peak concentration rapidly after the switch to the CO mixture, but it decayed slowly once CO was removed. Because of these effects, collection of the expired gas commenced on inspiration of CO and was stopped six complete breaths after CO was switched off. For the recording shown in Fig. 2, the period of exposure to CO was 58 s and the period of the collection of the expired gas was 89 s. The remaining traces in Fig. 2 show the dry fractional concentration of N_2, followed by the subject's ECG and the dry fractional concentrations of CO_2 and O_2. The slight cyclic variation of N_2 shown in Fig. 2 is in accordance with the known small increase in N_2 concentration for alveolar air compared with ambient air in steady state due to the respiratory quotient effect (5). It is also noted that the mask pressure and the expiratory flow lead the corresponding traces of gas concentration by ~0.5 s. This lead time reflects the delay in drawing the sampled gas to the mass spectrometer and its subsequent analysis.

Comparison between exposures to 1,500 and 7,500 ppm CO. The means of the measured and derived results for the 55 subject exposures for each CO concentration are summarized in Table 1. Mean values for each subject, which are not shown, were obtained by separately averaging the measured and predicted values for the five exposures per CO profile. In general, the variability among the subjects, represented by means ± SD, was much larger than that found between exposures for individual subjects.

Collected gas temperature and barometric pressure remained essentially the same for the two CO concentrations. The mean exposure times (t_e) aimed for were achieved. The t_c's were ~30 s longer than the mean exposure times due to the extra time required to collect the expired gas from the six additional breaths following the exposure. The parameter f, listed in Table 1, is the frequency of breathing over the exposure period.

The mean $F_{I_{CO}}$ for both CO concentrations was ~5% less than targeted; however, the values of 1,500 and 7,500 ppm CO were nominally assigned, and the values used for analysis were those actually recorded. Mean $F_{A_{CO_2}}$ levels were nearly the same for the two concentrations of CO, and for $F_{E_{CO_2}}$, the two mean values were virtually identical. Also, the values of $F_{A_{CO_2}}$ and $F_{E_{CO_2}}$ during nonexposure periods (not shown in Table 1) were essentially the same as those measured during the CO exposures. The mean values of $\dot{V}_E$, $\dot{V}_{CO_2}$, $\dot{V}_A$, and steady-state $D_{L_{CO}}$ were consistent for the two concentrations of CO used.

The means of the measured HbCO% values for the five exposures to the two CO concentrations are illustrated in Fig. 3. The subjects began with essentially the same initial level of HbCO% in both cases. Although the SE increased with increased measured HbCO% value, the relative variation (i.e., the ratio of SE to mean value) was ~4.3% and remained nearly constant. Thus the variability in measured HbCO% among subjects did not change appreciably with increasing value of HbCO%. The mean ± SE HbCO% levels at 37 min for the 1,500-

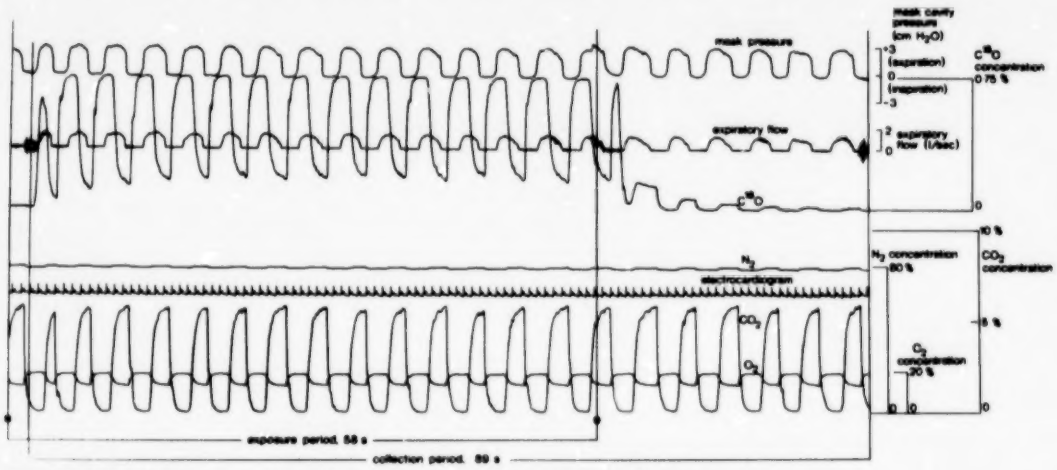

FIG. 2. Recording of ventilatory functions and gases for a particular 7,500 ppm CO exposure.

TABLE 1. *Measured and derived results*

Parameters	Concentration of CO, ppm	
	1,500	7,500
T, °C	22.6±1.1	22.8±0.8
P_B, Torr	744±3	745±3
t_e, min	5.00±0.02	1.00±0.02
t_c, min	5.46±0.13	1.52±0.13
f, breaths/min	13.8±3.0	12.9±3.0
$F_{I_{CO}}$, ppm	1431±41	7216±115
$F_{A_{CO}}$, ppm	320±39	1532±192
$F_{A_{CO_2}}$, %	5.83±0.18	5.81±0.32
$F_{E_{CO_2}}$, %	3.71±0.24	3.72±0.40
V_E, l ATPS	38.59±5.96	10.16±1.14
$\dot{V}_E$, l BTPS/min	7.72±1.24	7.36±1.05
$\dot{V}_{CO_2}$, ml STPD/min	235±31	225±35
$\dot{V}_A$, l BTPS/min	4.87±0.67	4.72±0.76
$D_{L_{CO}}$, ml STPD·min^{-1}·Torr^{-1}	20.3±4.5	20.4±3.2
Hb, g/100 ml blood	14.27±0.80	14.49±0.73
ΔHbCO, %/exposure	2.08±0.27	2.05±0.29

Values are means ± SD; n = 11. T, temperature; P_B, barometric pressure; t_e, exposure time; t_c, collection time; f, breath frequency; $F_{I_{CO}}$, concentration of inspired CO; $F_{A_{CO}}$, concentration of alveolar CO; $F_{A_{CO_2}}$, concentration of alveolar CO_2; $F_{E_{CO_2}}$, concentration of mixed-expired CO_2; V_E, volume of expired gas; $\dot{V}_E$, minute ventilation; $\dot{V}_{CO_2}$, CO_2 production; $\dot{V}_A$, alveolar ventilation; $D_{L_{CO}}$, pulmonary diffusing capacity; Hb, hemoglobin; ΔHbCO%, change in percent carboxyhemoglobin.

and 7,500-ppm exposures were 11.46 ± 0.41 and 11.13 ± 0.45%, respectively, and were statistically not different. Change in HbCO% (ΔHbCO%), as determined by gas chromatography, is the increase in HbCO% per exposure using the measurements made 2 min after and 1 min before the CO exposures. For a single concentration of CO, there was no significant difference among ΔHbCO% for the five exposures when the effects of variations in $\dot{V}_A$ and mean inspired CO tension were accounted for. The mean ΔHbCO% for these five exposures is shown in Table 1. There is no statistical difference between ΔHbCO% of 2.08 and 2.05% for inspired CO concentrations of 1,500 and 7,500 ppm.

CFK model prediction. The means of the predicted HbCO% values for all subjects at each of the five exposures to the concentrations of 1,500 ppm CO and 7,500 ppm CO are shown in Figs. 4 and 5. Although the steady-state value of $P_{I_{CO}}$ used for the predictions overestimated the concentration of CO in the initial breath and did not take into account the residual CO once the CO inspirate was switched off (see Fig. 2), the integrated dose of all the CO inspired closely approximated a constant level of $P_{I_{CO}}$ over the exposure period. It is this level of $P_{I_{CO}}$, as determined by *Eq. 7*, that was applied to the CFK model for each exposure. The predicted values of HbCO% lie within the SE of the measured values at the end of the five exposures. The means ± SE predicted values for HbCO% were 11.63 ± 0.59 and 11.46 ± 0.49% immediately after the fifth exposure to 1,500 and 7,500 ppm CO, respectively.

DISCUSSION

Respiratory parameters. The means for most of the measured and predicted respiratory parameters shown in Table 1 compared favorably with typical values for healthy resting young males (5). The mean value of the partial pressure of CO_2 in the end-tidal gas of our subjects was 40.6 Torr, confirming alveolar sampling and a respiratory steady-state condition. The mean value of $\dot{V}_A$ was ~4,800 ml BTPS/min, ~14% larger than the typical value of 4,200 ml BTPS/min (5). If 4,200 ml were used for $\dot{V}_A$ in the CFK equation instead of the measured value, the resultant mean increase in HbCO would be underpredicted by ~10%.

The mean steady-state value of $D_{L_{CO}}$ was 20.4 ml STPD·min^{-1}·Torr^{-1}. This agrees with the steady-state values reported by others, 16.9 (6) and 23.5 ml STPD·min^{-1}·Torr^{-1} (15), although these were measured in completely recumbent subjects.

Although each subject's mean value of $D_{L_{CO}}$ over the five exposures was used to predict HbCO%, a small decrease in $D_{L_{CO}}$ might be expected with increasing HbCO% (13). We observed an overall decrease in mean $D_{L_{CO}}$ from the first to the last exposure, which was consistent with the reported decrease of ~1% in the base-line value for each percent increase in blood HbCO% (13). Not correcting for this decrease did not

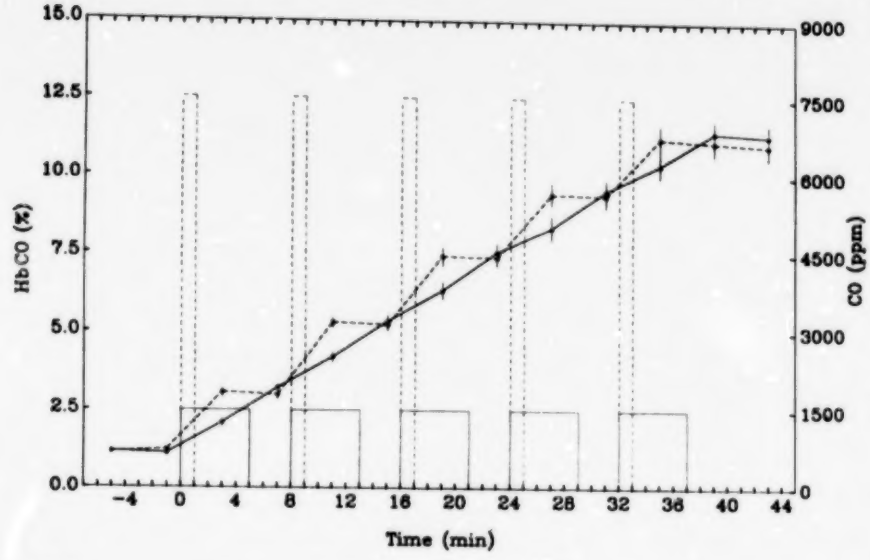

FIG. 3. Mean (±SE) (n = 11) of all measured percent carboxyhemoglobin (HbCO%) connected by *solid lines* for exposures to 1,500 ppm CO and by *dashed lines* for exposures to 7,500 ppm CO. CO exposure profiles are indicated by corresponding *light solid* and *dashed lines*.

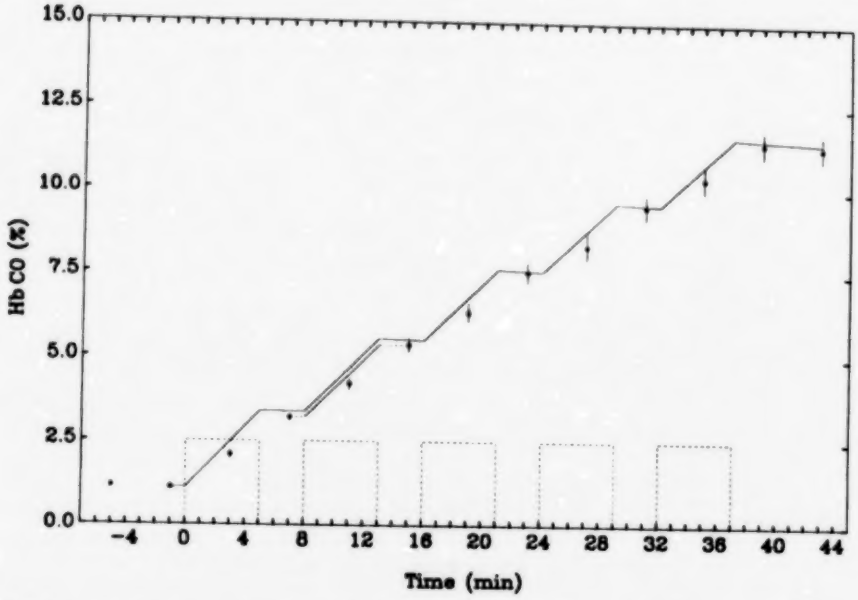

FIG. 4. Mean measured percent carboxyhemoglobin (HbCO%) (±SE) (*filled circles*; n = 11) and mean predicted HbCO% (*solid lines*) for exposures to 1,500 ppm CO (*dashed lines*). Predicted values begin with mean measured value 1 min before first exposure. Prediction indicated by *dashed-solid line* for second exposure begins with measured HbCO% 1 min before exposure.

lead to serious error in the prediction of CO uptake at the end of the five exposures. This is because a slightly larger uptake of CO predicted for the first exposure and a slightly reduced uptake of CO predicted for the last exposure were approximately balanced by using the subject's mean $D_{L_{CO}}$ value throughout.

Uptake of CO. Once exposure to CO began, at least four breaths were required before a steady-state condition was reached (see Fig. 2). This rate of equilibration appears to be exponential, as predicted previously (3, 7). The time constant for this equilibration, calculated from the mean value of the measurements, was 0.34 min. This represents about four to five breaths; 95% equilibration is predicted to occur after six breaths, in concurrence with the observation.

In addition, the fractional CO uptake determined by the steady-state method was 49.9% based on the mean values given in Table 1. This compares well with the typical value of 53% for resting subjects (5).

Rate of HbCO formation. It is noteworthy that after every exposure to 7,500 ppm CO, the second blood sample drawn showed a decrease in HbCO% (see Fig. 3). The probability of such an event occurring by chance is 1/25. This suggests that for the first blood sample drawn after each exposure, 2 min was sufficient for the inhaled CO to be absorbed, circulated, and mixed in the blood. If this time were insufficient, one would expect to see a further increase in HbCO% in the blood sample drawn 4 min later. Furthermore, if the HbCO% measured 2 min after the CO exposure had not reached or approached the peak value, then the predicted slope of diminishing HbCO would probably not agree with the measured slope. Since

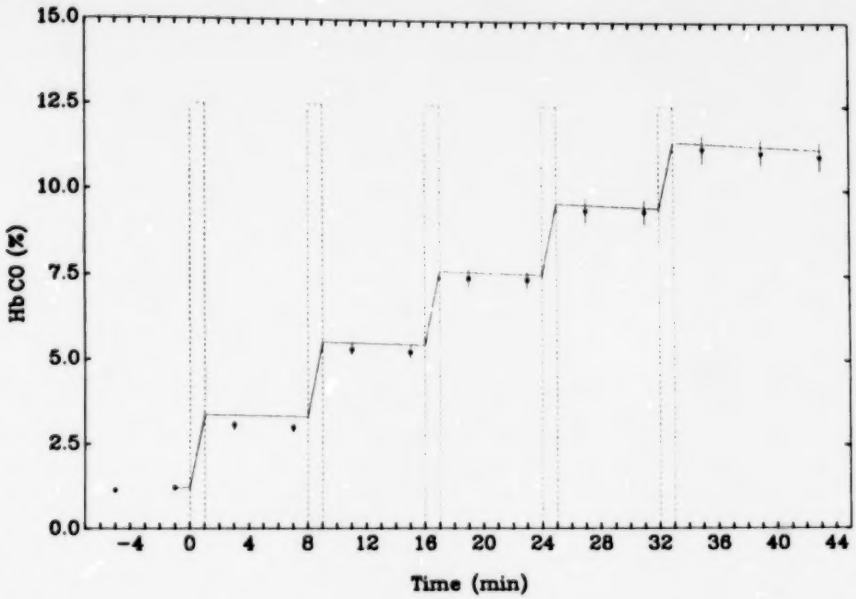

FIG. 5. Mean measured values (±SE) (*filled circles*; n = 11) and mean predicted percent carboxyhemoglobin HbCO% (*solid lines*) for exposures to 7,500 ppm CO (*dashed lines*). Predicted values begin with mean measured value 1 min before 1st exposure.

the measured and predicted slopes do agree well (see Fig. 5), it is concluded that a wait of 2 min is sufficient to measure the resultant HbCO% from a completed CO exposure in resting subjects.

The total amount of CO inhaled by our subjects in the two experiments with different CO concentrations was nearly equal, and the resultant measured HbCO% was similar. However, according to *Eq. 1*, there should theoretically be a different resultant HbCO% immediately on termination of the exposure when the concentration of CO varies, even though the total dose may be the same. This is because, while overall HbCO% is increasing during the exposure period, a portion of HbCO will be dissociating. The rate of this dissociation and the elimination of CO is expressed in the time constant. *Equation 1* predicts an increase in HbCO% of 2.24% after a 1-min exposure to 7,500 ppm CO and 2.22% after a 5-min exposure to 1,500 ppm CO in this study using mean data. After the 5-min period, more CO will have been eliminated. However, because the time constant for CO is relatively long, the difference of 0.02% between these two predictions is negligible. Therefore, when the subject is exposed to CO for a short period of time, a prediction of his resultant HbCO can be approximated very well given only the total dose received. It is inconsequential whether the exposure is of high concentration and short duration, of low concentration and long duration (but well within the time constant for CO uptake and elimination[1]), or saw-toothed, provided that the total dose is the same. Under normal ventilatory conditions, this offers the practical advantage of applying only the integrated dose from CO exposure rather than the actual concentration profile to the CFK model.

[1] As a first approximation (taking the linear form of the CFK equation), the time constant for CO uptake and elimination in resting subjects is about 550 min. Therefore, exposures to different CO levels and of <1 h in duration but of equal total dose result in practically the same final HbCO.

An inherent limitation of the CFK model is the prediction of instantaneous uptake and mixing of CO, and formation of HbCO. No delay in the increase of HbCO% due to the time required for the onset of steady-state pulmonary gas exchange conditions or owing to the circulation of blood is accounted for. Thus the HbCO% measured when CO is being breathed should be less than that predicted at the time of the measurement. This was indeed the case as can be seen in Fig. 4. If one extrapolates the pre- and the postexposure measured values of HbCO% to the start and end of an exposure, respectively, and these two points connected as shown by the dashed-solid line for the second exposure in Fig. 4, it is seen that the HbCO% measured during the exposure falls below the overall predicted HbCO% profile. This dashed-solid line, in fact, represents the predicted rate of HbCO formation starting from the HbCO% value measured 1 min before the second exposure. The predicted rate of HbCO% increase is nearly linear for the levels of HbCO% considered here. The actual rate of appearance of HbCO at the point where the blood is drawn is unknown; however, it is likely sigmoidal in shape. The present result gives some indication of the magnitude of the delayed increase of HbCO% during exposure to CO in the resting subject.

Effective blood volume. Although the overprediction of HbCO% after the exposures to CO shown in Figs. 4 and 5 was not large compared with the measured values, it was nevertheless consistent for both CO concentrations. This slight overprediction may be explained, in part, by the absorption of CO by body stores other than blood. This involvement of extravascular stores in the binding of CO would appear as a larger effective blood volume and result in a lower measured HbCO%, as discussed by Coburn et al. (4). (In the present study, the mean anthropometric estimate of blood volume of the subjects was 5,140 ± 487 ml.) The extent to which extravascular

stores are involved is a matter of conjecture, since the equilibration time between intravascular and extravascular CO may take as long as 60 min (4). Consequently, at the end of the experiment, CO absorbed during the first exposure would be nearly equilibrated with extravascular stores, yet CO absorbed during the last exposure would be almost entirely still in the blood. Although the net amount of CO in equilibrium between intravascular and extravascular stores was not known at the end of the experiment, this mechanism could contribute to the slight overprediction of HbCO% noted in Figs. 4 and 5.

CONCLUSION

The increase in HbCO% resulting from two exposures to CO differing in inspired concentration and timing, but similar in total dose, was not significantly different. The higher the CO concentration, the greater is the rate of increase of HbCO%, but the resultant HbCO% is practically the same for the same amount of CO inhaled over short durations.

The prediction of the HbCO% level using measured values of $\dot{V}_A$ in the CFK equation agrees with the measured results in resting subjects exposed to high transient CO concentrations. Since the prediction of the increase in HbCO% is sensitive to the value of $\dot{V}_A$, a serious error could result if the values applied in the equation were assumed and/or expressed in BTPS rather than STPD units.

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